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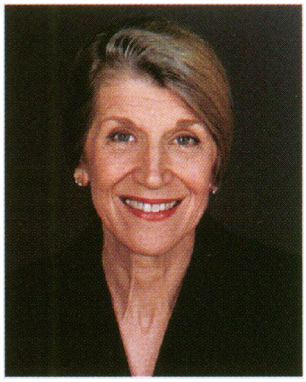
Carcinogen Risk Assessment Guidelines and Children



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Over two years ago, the White House issued Executive Order 13045, "Protection of Children from Environmental Health Risks and Safety Risks," which called upon federal agencies to identify and assess environmental health and safety risks that may disproportionately affect children and to ensure that their policies, programs, and standards address these risks (*1*). The executive order reflected a growing emphasis on well-recognized differences in the exposures, metabolism, and disease responses of infants and children to chemical exposures.

Concern about the special vulnerability of infants and children to environmental exposures, particularly pesticides, prompted the U.S. Congress in 1988 to request that the National Academy of Sciences study this issue. This study resulted in the important 1993 report *Pesticides in the Diet of Infants and Children* (*2*). In its National Agenda to Protect Children from Environmental Health Threats, the U.S. Environmental Protection Agency (EPA) committed itself to ensuring that all standards it adopts will protect children (*3*). In 1997, the EPA solicited comments from the public on which standards to reevaluate to assess special needs of children, and a national advisory committee identified several topics—mercury emissions, protection from farm chemicals, atrazine in food and water, and organophosphate and carbamate pesticides (*4*).

The focus on children is reengaging the public health community in the environmental health arena after a period of seeming indifference. This shift, coupled with a renewed emphasis on the safety of food and water supplies, represents a renaissance for environmental health and an important challenge. The protection of children will require, among other things, that guidelines for carcinogen risk assessment address children.

These concerns make the proposed revised EPA guidelines for carcinogen risk assessment of particular interest. It is important to ensure that the guidelines address cancer risks for children and to protect children and infants. The most recent draft of the guidelines was issued in 1996 (*5*). The draft was released before adoption of the executive order and did not include any direct mention of how to assess the particular needs of children. This draft remains under review.

Federal policy has one example of a statute written with the intent of providing special protections for infants and children. The Food Quality Protection Act (FQPA) (*6*), passed in 1996 by a unanimous vote of the Congress, amended federal laws regarding pesticides in two ways that were particularly important for children. First, the statute requires that when allowable levels of pesticides for foods are set, special protections be provided for children. The statute recognizes that the exposure of children may differ from that of adults and, in this case, mandates collection of data about food consumption patterns of children (section 301). It incorporates scientific principles in mandating that all routes of exposure to pesticides be considered in assessing risk (section 405). Second, federal agencies are to consider whether infants and children may be disproportionately susceptible to pesticides and to consider the potential for combined impacts of chemicals with common mechanisms of action. These are important new principles for scientifically grounded policy that will be protective of children. When data are not adequate to allow for assessment of differences in exposure and susceptibility for children, pesticide tolerances are to incorporate an additional safety factor of 10. Although the process of implementation of these fundamental new directions may be difficult and will require adjustment both by regulatory agencies and by pesticide users and producers, these important policy goals are worthy of consideration in the context of guidelines for risk assessment for chemical carcinogens.

Toxic responses in infants and children can differ markedly from those seen in adults, both in severity and in the nature of the adverse effect. During the growth and maturation process there is an evolution of membranes, including receptors, in infants and children as they approach adulthood. These changes represent a potential for a very different environment for chemical and drug interactions with receptors. Examples of differences in drug–receptor interactions between children and adults are provided by the paradoxical responses to phenobarbital and Ritalin in children versus adults. Phenobarbital, a sedative in adults, produces hyperactivity in children, whereas Ritalin, which is used as an antihyperactive agent in children, produces an opposite effect in adults. The explanation for these widely differing responses in children and adults is believed to reside in differences in receptor–drug interactions (*7*).

Differences in the developing infant and child also effect absorption, dose, distribution, biotransformation, storage, and excretion of chemicals or drugs in the body, and therefore toxicity (*7*). Of particular interest are the enzymes involved in metabolism of toxic compounds. The enzymes important to both phase I transformation through the cytochrome P450 system and phase 2 transformation can vary with age (*8*).This variability can result in differences in sensitivity to the toxic effects of pharmacologic agents and xenobiotics. Moreover, children may also have less capacity to repair damage.

Perhaps the most distinguishing characteristic of infants and children is that they grow and develop. Different systems and organs develop at different rates and at different phases (*9*). Children may be more vulnerable to chemical exposures that affect growing tissue. A critical period for exposure to radiation in the mammary gland is the period during adolescence when cells are proliferating.

Studies of effects of radiation provide evidence of increased susceptibility of those exposed during childhood (*10*). Among the survivors of radiation from the exploding of the atomic bomb, susceptibility to leukemia was greater for those who were under 20 years of age when exposed as compared to those who were older. Moreover, the type of leukemia developed varied by age at exposure. For breast cancer, risk also varied by age of exposure and was highest for those

who were under 20 years of age. The rate of excess risk decreased with age up to 39 years and was significantly lower for those 40 years of age or older when exposed. Studies of exposure to cigarette smoke have shown that the risk of dying of breast cancer is greater for those who started smoking before age 16 than for those who started smoking after age 20 (*11*).

Issues of concern pertain to all steps in the risk assessment process. The first step in risk assessment, hazard identification, is to decide what agents merit detailed review. In considering whether risk assessment approaches are protective for children, an initial question is whether methods for hazard identification would capture the agents of concern for children. The major sources of information for hazard identification are animal bioassays and epidemiologic studies. An important question to review for carcinogen risk assessment is whether these data sources are adequate to identify agents that would pose particular risks for children.

Some attention has been given to this issue. One approach is to consider expanding the scope of protocols for animal assays to incorporate perinatal exposures. As part of a 1992 conference on risk assessment for children, it was concluded that animal bioassays which included perinatal exposures did not detect carcinogens that were not identified through standard methods (*12*). A more recent review prepared by the EPA for the Science Advisory Panel, which is charged with reviewing the scientific basis for pesticide policy, came to a different conclusion (*13*), although the analysis has not yet been reviewed by the Science Advisory Panel. The question of whether current data sources are adequate to identify agents that pose particular risks for children should be carefully considered in the development of new guidelines for risk assessment.

For epidemiologic studies, additional attention to studies of *in utero*, perinatal, and childhood exposure is needed. Data used for risk assessment are often based on studies of healthy adult males.

Infants and children differ from adults in their exposures both qualitatively and quantitatively, in part because they eat more food, drink more water, and breathe more air per unit of body weight than adults do (*7*). For example, the air intake of a resting infant is twice that of an adult under the same conditions (*9*), and the activity patterns of children further increase their exposure to pollutants. Because children are typically engaged in more physical activity, play close to the ground, and engage in characteristic hand-to-mouth behavior, they are exposed to higher levels of toxicants such as pesticides, radon, and particulate matter (*14*). The micro- and macroenvironments for infants and children change through development. Additionally, these environments may vary by demographic or cultural group, and these differences may influence exposure.

For exposure assessment of infants and children, their environment must be defined and their behavior must be linked to the time spent in different environments such as home, daycare, or school and how this varies by age. Exposure research is needed to describe how children's typical activities and environments differ from those of adults and what contaminant levels are associated with these activities and environments. Currently, the data needed for exposure assessment of infants and children are seriously lacking.

Differences in the rate of movement of a drug or chemical through the body of an infant or child as compared to an adult will affect the dose rate as well as the type and degree of adverse effects observed. Such differences are well documented for absorption by inhalation, ingestion, and dermal contact, and appear to be related to differences in tissue (membrane) composition, surface area, and/or perfusion. The composition of some membranes changes with maturation. These differences can exert significant influences on the quantity and rate of absorption of certain drugs and chemicals. Adjustments need to be made to dose estimates to account for differences of infants and children.

In the context of cancer risk assessment, an enduring controversy has been the approach of extrapolating results from high doses used in animal experiments to the lower doses experienced by humans. In the past, the risk assessment guidelines have used models that are linear in the low dose region (which represents environmental exposure) as a default. The EPA's approach has been to use the upper 95% confidence bound on the slope of the line generated by the linear model to estimate the potency of carcinogens. Such potencies are then used to estimate risks at various exposures. This approach is conservative in that it allows for variability in response among animals and it provides a more stable estimate than would an estimate of maximum likelihood. It does not, however, incorporate any provision for particular vulnerability of any human population (*9*).

One of the most important features in the proposal for new guidelines is the incorporation of greater emphasis on mechanisms for carcinogenic action. The EPA has proposed to depart from using linearized models to relate doses to responses when the mode of action is deemed not to be genotoxic. In these cases, the guidelines propose to use a benchmark dose approach to risk assessment. A benchmark approach uses a model to determine the dose that would result in a defined rate of an outcome, usually 5 or 10%. Safety factors can then be applied to this benchmark dose level. This approach does not incorporate the conservatism of the linear model.

A key question for development of guidelines that address issues of concern for children is how to ensure that the review of modes of action identifies all those that might be relevant to children. Because children's metabolic pathways and repair capacities are known to differ from those of adults, it is important to develop criteria to ensure that judgments made on modes of action reflect not just adult metabolism but also that of children. Admittedly, this will be a difficult undertaking, as evidence for modes of action often comes solely from rodents and poses difficulties of interpretation even for adults. But before methods of assessment that are protective of health are abandoned, we should ensure that the health of children is not being jeopardized.

As noted, children may be more vulnerable to effects of toxic compounds than adults receiving a comparable dose. Adjusting dose–response parameters for additional vulnerabilities of children is also an important step.

The differences in dose, vulnerability, and mechanisms of action between adults and children have not been adequately studied, and consequently there are few data to guide this aspect of carcinogen risk assessment for children. A recent review suggests that data are not likely to be available to support quantitative review (*15*). It would be appropriate for the new cancer risk assessment guidelines to address when to consider the potentially greater vulnerability of children and how this could be systematically incorporated into the assessment. For the development of reference doses for noncancer effects, an additional safety factor can be used to address variability in the human population. The FQPA (*6*) provides for an additional margin of safety when there is reason to believe there may be disproportionate impacts on children but inadequate information to evaluate them quantitatively. An equivalent approach for cancer risk is needed as well.

Risk assessment methods for carcinogens have not considered the timing of doses of carcinogens during a human lifetime. Models used to estimate dose and response do not consider the age at which doses are applied. A given dose of a carcinogen counts the same at 70 years of age as it does at 5. Because there is considerable evidence that doses received earlier in life are more likely to result in development of cancer than doses received late in life, this approach would be expected to underestimate risks of doses received during childhood. Moreover, recent evidence suggests that cancers experienced early in life are associated with adult medical problems in a large

percentage of cases. Effects of treatments typically used for cancer can include second malignancies, organ toxicity, effects on growth, endocrine effects, and reproductive effects (*16*). The new guidelines should give serious attention to doses received earlier in life, which can be expected to pose greater risks during the lifetime as a whole.

Currently, we simply do not have sufficient information regarding the differences in exposure, susceptibility, and toxicity for infants and children as compared to adults to accurately characterize the risk for most chemical exposures. The implications of this are manifold. We must aggressively pursue the research agenda outlined at the EPA conference (*14*) while simultaneously implementing policies that address the implications of the information gaps. We have no evidence to suggest that exposure standards based on assumptions about adult toxicity, susceptibility, and exposure will adequately protect infants and children. Quite the contrary, there is sufficient evidence for some agents to believe they may not. The proposed carcinogen risk assessment guidelines should incorporate language that will provide infants and children with needed protection. Continued emphasis should be given to exposure reduction.

The task ahead, to adapt the proposed carcinogen risk assessment guidelines to embrace the needs of infants and children for adequate protection, will no doubt face many challenges. Developing the science base will require a sustained effort of many disciplines, but developing the philosophic base may be equally or more challenging. The recent focus on human rights in schools of public health as a framework for public health ethics may provide some guidance and support.

Human rights organizations and community-based groups argue for the incorporation of human rights standards into public health policies. Even such fundamental human rights concepts as the right to health and the special duty to protect vulnerable populations have not been operationally defined in public health, and no scholarship in jurisprudence exists to describe the parameters of these rights (*17,18*). Nevertheless, there is a growing body of literature from which to draw in the areas of philosophy, public health, and biomedical ethics (*19,20*). The human rights perspective is valuable because it derives from an organized set of internationally recognized and forward-thinking legal standards (*21*).

Advancing public health policies without seriously considering their human rights dimensions may seriously limit their effectiveness and, in some instances, may even result in harm to individuals (*22*). While promulgating carcinogen risk assessment guidelines that do not adequately address the special exposures, susceptibility, and vulnerability of infants and children would be ineffective and possibly harmful, i.e., conveying a false sense of protection, it can be further argued that it would violate basic notions of human rights. All persons have a right to health, including a safe environment and protection from exposures that may undermine their health. For infants and children, who can not act on their own behalf, a special obligation is incurred. All potentially toxic exposures to which infants and children are exposed need to be assessed for their impact, and this information should be incorporated in carcinogen risk assessment.

It was community-based groups that advocated effectively for the children's environmental health agenda that is now on the table (*23*). They were correct to do so. It is also community organizations that lead the way in advocating for human rights concepts in the formulation of public health policies. We will need their help in addressing the challenges ahead.

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